PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Westbrook

Serial No.: 08/784,222

Filed: October 28, 1991

For: METHODS AND COMPOSITIONS FOR THE DETECTION OF CHROMOSOMAL ABERRATIONS

Examiner: D. Rees

Group Art Unit: 1807

Atty. Dkt: ARCD-010/PAR

CERTIFICATE OF MAILING
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October 4, 1996
Date

David L. Parker

AMENDMENT AND RESPONSE TO OFFICE ACTION MAILED JUNE 12, 1996

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The Examiner is requested to enter the following amendments. A response to the Office Action mailed June 12, 1996 is also submitted, along with a petition for a one month extension of time and the appropriate fee. The examiner is requested to consider the remarks therein. Re-examination is respectfully requested.

33. (New) The composition of claim 31 wherein the presence of said chromosomal aberration is diagnostic or prognostic for ALL and chronic myelogenous leukemia (CML).

RESPONSE TO OFFICE ACTION

Status of the Claims

Claims 1-20 and 24-29 have been amended. Claims 31-33 have been added. Claims 1-33 are presently in the case. A copy of the pending claims as amended is attached hereto as Exhibit A.

Rejection of Claims 1-30 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-30 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant wishes to thank the examiner for her many helpful suggestions. The examiner's specific objections are addressed below.

Claim 1 - The word "chromatin" and the phrases "sequences homologous with the probe sequences" and "detecting the presence of the probes" have been removed from the amended claim.

Claim 4 - The claim has been amended to show that the probes hybridize to sequences located approximately 800 kb apart in the aberrant chromosome.

Claim 6 - The claim has been modified as suggested by the examiner, to indicate that the labels are distinguishable under a microscope as different colors.

Claim 8 - The phrase "chromatin-probe contacts" is replaced with "probes hybridize with chromosomal DNA".

Claim 10 - The claim is modified to indicate that the probes after hybridization are juxtaposed as doublets if a chromosomal aberration is present. The redundant phrase "in interphase" is eliminated.

Claim 15 - The claim is modified to indicate that the fusion gene encodes a protein designated as p190.

Claim 17 - The plural "samples" and "tissues" have been changed to the singular "sample" and "tissue". The claim contemplates that single tissue samples from individual patients will be analyzed, although occasionally multiple samples from the same individual may be examined. The claim further contemplates that a given laboratory assay may include samples from more than one patient for efficiency. Claims 18 and 19 have been modified to correspond to the amended form of claim 17.

Claims 24-26 - These claims are modified to eliminate the word "designation".

Claim 29 - The phrase "appropriate controls" is replaced with "a control". It is recognized that one or more controls will be included in the kit.

With respect to the examiner's objections to claims 16, 21 and 23, applicant submits that it is fundamental patent law that claims are to be read in light of the specifications and both are to be read with a view to ascertaining the invention. *United States v. Adams*, 383 U.S. 39, 15 L. Ed.2d 572, 86 S. Ct. 708 (1966). The standard for § 112, second paragraph is whether one skilled in the art would be able to determine what subject matter is claimed. *Hybritech , Inc. vs. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986). Applicant submits that reading the specification and claims together, the skilled practitioner would be able to determine the claimed subject matter of claims 16, 21 and 23. The binding sites for PEM12 and c-H-abl are known in the art and are clearly identified in Fig. 2 of the instant specification. Probe MSB-1 is also clearly identified by binding site in Fig. 2 of the specification. The binding sites for these probes are also determinable from Tkachuk *et al.*, Science 250: 559-562 (1990).

Rejection of Claims 1-14, 16-20, 22, 23, 24 and 26 Under 35 U.S.C. § 102

The action has rejected claims 1-14, 16-20, 22, 23, 24 and 26 under 35 U.S.C. § 102(a) as being anticipated by Gray *et al.* EP 0 430 402 A2 (published 5/6/91) and under 35 U.S.C. 102(b) as being anticipated by Gray *et al.* CA 2021489, 1/20/1991. The action states that both references by Gray *et al.* teach the use of chromosomal probes c-hu-ABL and PEM12 to detect translocations generating a BCR-ABL fusion associated with CML.

The applicant submits that the Canadian patent cited by the examiner shows a publication date of 1/20/1991, not 1/20/1990. This is less than one year prior to the date that the present application was submitted. Therefore, this reference is not available under 35 U.S.C. §102(b) and applicant respectfully submits that a rejection of claims under § 102(b) is improper. The examiner is requested to particularly point out the basis for concluding that this reference was published more than one year before the application date of the instant invention.

Both references by Gray *et al.* acknowledge that Dr. Westbrook is the inventor of probes PEM12 and c-Hu-ABL. (See, for example, pg. 105, Section VIII of CA 2021489, 1/20/1991. See corresponding Section VIII of EP 0 430 402 A2, 5/6/91.) The present application has been amended to prosecute composition claims involving probes PEM12, c-Hu-ABL and MSB-1, rather than methods for detecting the BCR-ABL fusion. Support for this amendment is found throughout the Specification. (See Specification at page 8, line 32 through page 32, line 32.) Applicant respectfully notes that neither of the Gray references cited as prior art claimed these probes as compositions.

Since Gray *et al.* specifically acknowledge Dr. Westbrook as the inventor of these probes and the § 102 rejections rely solely upon the references by Gray *et al.*, applicant respectfully requests that these rejections be withdrawn. It is established patent law that an inventor's own prior work will not anticipate her later invention, absent a statutory bar. *E.g., In re Katz*, 215 USPQ 14 (CCPA 1982).

Although Gray *et al.* acknowledge Dr. Westbrook as the inventor of the probes, applicant is willing to submit a declaration under Rule 131 in support of her prior invention of the composition. However, applicant respectfully submits that a Rule 131 declaration is not necessary when there is uncontroverted evidence, provided in the cited references by Gray *et al.*,

that Dr. Westbrook is the only inventor of the claimed composition. *In re* Mathews, 161 USPQ 276 (CCPA 1969). Both cited prior art references acknowledge on their face that Dr. Westbrook is the inventor of the probes that are the subject matter of the present composition claims. Therefore, this subject matter cannot be the work of "another" and the cited prior art references cannot support a rejection under § 102(a).

The examiner has already acknowledged that claims 15, 21, 25 and 27-30 are not anticipated by Gray *et al.* Applicant submits that since the composition of probes comprising the instant application were acknowledged by Gray *et al.* to be the invention of Dr. Westbrook, no claims of the instant invention are anticipated. For these reasons, applicant submits that the instant invention does not "read on" Gray *et al.* and rejection of the claims under 35 U.S.C. § 102 is improper. Reconsideration of the claims is respectfully requested.

Rejection of Claims 1-30 Under 35 U.S.C. § 103

The action has rejected claims 1-30 under 35 U.S.C. § 103 as being unpatentable over Gray *et al.* in view of Bartram *et al.* (1987) and Blennerhassett *et al.* (1988). The examiner notes that Gray *et al.* teach the use of probes c-hu-ABL and PEM 12 to detect a BCR-ABL fusion gene that encodes the p210 protein. Bartram *et al.* teaches the use of probes to the 5' part of the major breakpoint cluster to detect different classes of CML. Applicant respectively traverses the assertion that Blennerhassett teaches the molecular characterization of breakpoints that result in the production of the p190 protein and teaches probes that hybridize to the first exon region of BCR, equivalent to a probe "designated as MSB-1". Applicant's detailed response to the 35 U.S.C. § 103 rejection is described below.

Applicant reiterates that the references by Gray *et al.* cannot constitute prior art against the instant application, since the probes disclosed by Gray *et al.* were in fact the invention of Dr. Westbrook, the present applicant. Applicant emphasizes that neither reference by Gray *et al.* is available under 35 U.S.C. § 102(b). Since these references are only available under 35 U.S.C. §102(a) and they acknowledge that the probes disclosed are the invention of Dr. Westbrook, neither reference by Gray *et al.* is available as prior art under 35 U.S.C. § 103. Without the information disclosed by Gray *et al.*, there is no suggestion in either Bartram or Blennerhassett that would lead a knowledgeable practitioner of the art to the instant invention.

Neither Bartram nor Blennerhassett teach the use of complex genomic probes that bind on either side of the breakpoint, resulting in juxtaposed doublets when a chromosomal aberration is present. There is no suggestion in either Bartram or Blennerhassett of a motivation for the skilled practitioner to develop such probes. The ^{32}P labeling technique used by Bartram and Blennerhassett is not even adaptable to detect juxtaposed doublets. There is no way that a skilled practitioner could have taken the teachings of Bartram and Blennerhassett and obtained the instant invention. Therefore, in the absence of the Gray *et al.* references, the instant invention is non-obvious and rejection of claims 1-30 under 35 U.S.C. § 103 is improper.

Even considering the Gray *et al.* references, applicant submits that the instant invention is non-obvious. A critical feature of the instant invention is that it provides probes to two <u>different</u> portions of the BCR gene, as well as a probe to the ABL gene, to perform chromosomal hybridization experiments. This allows the clinical differentiation of two distinct types of BCR-ABL fusion (hereinafter referred to as the p190 fusion gene and p210 fusion gene), resulting in the production of proteins p190 and p210. While most forms of CML involve the p210 fusion gene, a significant result of the instant invention is that it demonstrates the p190 fusion gene

occurs in a significant percentage of cases of ALL. None of the references cited by the examiner addresses the detection of the p190 fusion gene in ALL.

Gray *et al.* do not even teach that a p190 fusion gene occurs in leukemia. Blennerhassett teaches that a p190 fusion gene can occur in ALL. However, they do not teach probes that can distinguish between the p190 and p210 fusion genes. Blennerhassett only teaches probes to detect the p210 fusion gene. While Bartram teaches a probe capable of detecting a p190 fusion gene, they only apply this technique to CML, not to ALL. Further, as discussed below, the probe used by Bartram binds significantly downstream of the binding site for the MSB-1 probe of the instant invention and would potentially miss recombination events occurring in ALL. There is no teaching of record to indicate that any combination of probes can detect genetic recombinations occurring in a high percentage of ALL patients, using the MSB-1 probe claimed in the instant application or its equivalent.

It is significant that the MSB-1 probe of the instant invention binds to exon 1 of the BCR gene. Thus, it is capable of detecting all BCR-ABL fusions that could predispose to CML or ALL. As noted by the examiner, Bartram *et al.* teaches probes to the 5' part of the major breakpoint cluster. Figure 2(a) on pg. 507 of Bartram demonstrates that this probe is only 15 kb 5' to the bcr region. (According to the scale of Fig. 2(a), 3 mm = 0.1 kb, and the 5' end of the probe is located 4.5 cm 5' to the bcr.) Figure 2 of the Specification in the instant application shows that the MSB-1 probe binds at least 50 kb 5' to the bcr region. (The entire BCR gene, measuring 15.5 cm in Fig. 2, is 130 kb long. Specification at pg. 20, line 11. The MSB-1 binding site extends 6 cm 5' of the PEM12 binding site, which in turn is located at the 5' end of the bcr region.)

There is no equivalency between the 5' probe taught by Bartram *et al.* and the MSB-1 probe taught in the instant invention. They are two distinct, nonoverlapping probes. The teaching of Bartram could not have made either the MSB-1 probe obvious, since Bartram did not teach how to make or use this probe, nor did they teach any method for obtaining the MSB-1 probe. Bartram *et al.* do not even suggest that it would be desirable to obtain a probe such as MSB-1.

The Office Action states that Blennerhassett "teaches probes that hybridize to the first exon region (interpreted here...to be equivalent to a probe 'designated as MSB-1')." Applicant respectfully traverses this assertion and requests that the examiner specifically point out where in Blennerhassett such teaching is to be found. The phl/bcr-3 probe described by Blennerhassett is only capable of detecting the p210 fusion gene, not the p190 fusion gene. (See pg. 649, 2nd column, last paragraph - this probe "was designed to detect all Ph(**bcr-210**) translocations.") This probe hybridizes to sequences located between small coding exons 1 and 2 <u>of the bcr region</u>. This is not the same as exon 1 of the BCR gene, where the binding site for the MSB-1 probe is located. For the reasons stated in the immediately preceding paragraph, applicant submits that Blennerhassett in no way makes the instant invention obvious.

There is no teaching in Gray *et al.*, Bartram *et al.* or Blennerhassett *et al.* that would provide a skilled practitioner with either the guidance or motivation to make and use the instant invention. There is no suggestion in any of these references as to how a practitioner would obtain the MSB-1 probe or its equivalent. Therefore, these references cannot have provided a practitioner with the motivation to develop the instant invention. In the absence of such motivation, the cited references only provide a mere "invitation to experiment" that cannot support an obviousness rejection. *In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

For the reasons stated above, applicant respectfully submits that the examiner has failed to establish a *prima facie* case for obviousness. Applicant requests that the rejected claims be reconsidered in light of this argument.

Double Patenting

The action rejected claims 1-30 under 35 U.S.C. § 101 for statutory type double patenting. The claims of the present application have been amended so that they are no longer coextensive in scope with copending application Serial No. 08466781. Specifically, the claims of the present application have been amended to composition claims, while copending application Serial No. 08466781 is drawn to methods claims.

Since the claims of the copending applications are no longer coextensive in scope, applicant respectfully requests that the rejected claims be reconsidered in light of their amendment.

Summary and Conclusion

In light of the foregoing comments, applicant submits that all pending claims are in condition for allowance and solicit an early indication to that effect. Should Examiner Rees feel that further discussion of any of the issues is merited, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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